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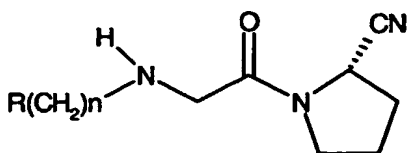
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- Published:**
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: THE USE OF SUBSTITUTED CYANOPYRROLIDINES AND COMBINATION PREPARATIONS CONTAINING THEM FOR TREATING HYPERLIPIDEMIA AND ASSOCIATED DISEASES



(I)

(57) Abstract: Disclosed are methods and compositions for the treatment of hyperlipidemia and conditions associated therewith, such as CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia and post-prandial lipemia. The methods include administration of a therapeutically effective amount of a compound of formula (I), wherein R is substituted adamantyl; and N is 0 to 3; in free form or in acid addition salt form, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05762

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/40 A61K45/06 A61P9/10		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) CHEM ABS Data, EMBASE, BIOSIS, MEDLINE, EPO-Internal, PAJ, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 34241 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); VILLHAUER EDWIN BE) 15 June 2000 (2000-06-15) cited in the application page 7, paragraph 2 page 8, paragraph 2 -page 9, paragraph 3 example 1 claims 1-9	1-17
X	US 6 011 155 A (VILLHAUER EDWIN BERNARD) 4 January 2000 (2000-01-04) examples 47,49,53 claims 5,9,10	3
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<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
24 September 2003	01/10/2003	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer van der Kooij, M	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05762

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 166 063 A (VILLHAUER EDWIN BERNARD) 26 December 2000 (2000-12-26) cited in the application example 1 claims 1-9 ---	3
P,X	WO 03 038123 A (NOVARTIS PHARMA GMBH ;NOVARTIS AG (CH); LAVEDAN CHRISTIAN NICOLAS) 8 May 2003 (2003-05-08) page 23, paragraph 1 page 45, paragraph 1 -page 46, paragraph 3 ---	1-3,5-7
A	EP 1 125 922 A (WELFIDE CORP) 22 August 2001 (2001-08-22) the whole document ---	1-17
A	EP 0 187 052 A (PANMEDICA SA) 9 July 1986 (1986-07-09) page 24, line 28 - line 35 claims 1-19 -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/05762

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1, 5-9 and 11-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 9-17 relate to the treatment of a disease which actually is not well defined.

The use of the definition "lowering LDL, Lp(a) and/or VLDL levels in a mammal" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the disease for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful search over the whole scope of the claims impossible.

Consequently, the search has been restricted to the real and defined disease states mentioned in claim 1 and 7, i.e. hyperlipidemia, atherosclerosis, angina pectoris, carotid artery disease, cerebral arteriosclerosis, xanthoma, CHD, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudification, myocardial infarction, dyslipidemia and post-prandial lipemia.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/05762

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0034241	A	15-06-2000	AU 759773 B2	01-05-2003
			AU 1658000 A	26-06-2000
			BR 9915985 A	04-09-2001
			CA 2350609 A1	15-06-2000
			CN 1329593 T	02-01-2002
			CZ 20012028 A3	12-09-2001
			WO 0034241 A1	15-06-2000
			EP 1137635 A1	04-10-2001
			HU 0104495 A2	29-04-2002
			JP 2002531547 T	24-09-2002
			NO 20012853 A	07-08-2001
			PL 348043 A1	06-05-2002
			SK 7892001 A3	06-11-2001
			TR 200101478 T2	22-10-2001
			TW 509674 B	11-11-2002
			US 6166063 A	26-12-2000
			ZA 200104581 A	22-05-2002
US 6011155	A	04-01-2000	US 6124305 A	26-09-2000
US 6166063	A	26-12-2000	AU 759773 B2	01-05-2003
			AU 1658000 A	26-06-2000
			BR 9915985 A	04-09-2001
			CA 2350609 A1	15-06-2000
			CN 1329593 T	02-01-2002
			CZ 20012028 A3	12-09-2001
			WO 0034241 A1	15-06-2000
			EP 1137635 A1	04-10-2001
			HU 0104495 A2	29-04-2002
			JP 2002531547 T	24-09-2002
			NO 20012853 A	07-08-2001
			PL 348043 A1	06-05-2002
			SK 7892001 A3	06-11-2001
			TR 200101478 T2	22-10-2001
			TW 509674 B	11-11-2002
			ZA 200104581 A	22-05-2002
WO 03038123	A	08-05-2003	WO 03038123 A2	08-05-2003
EP 1125922	A	22-08-2001	AU 6367399 A	22-05-2000
			CA 2348879 A1	11-05-2000
			EP 1125922 A1	22-08-2001
			US 6468998 B1	22-10-2002
			CN 1332726 T	23-01-2002
			WO 0026186 A1	11-05-2000
EP 0187052	A	09-07-1986	FR 2572399 A1	02-05-1986
			AT 49957 T	15-02-1990
			AU 583543 B2	04-05-1989
			AU 4884685 A	08-05-1986
			DE 3575715 D1	08-03-1990
			EP 0187052 A1	09-07-1986
			ES 8702888 A1	01-04-1987
			JP 61109766 A	28-05-1986
			KR 9203837 B1	15-05-1992
			US 4661512 A	28-04-1987
			ZA 8508169 A	25-06-1986